(12) UK Patent Application (19) GB (11) 2469883 (13) A

(43) Date of A Publication 03.11.2010

(21) Application No: 0908006.0

(22) Date of Filing: 30.04.2009

(71) Applicant(s):
Sandoz AG
(Incorporated in Switzerland)
Lichstrasse 35, CH-4056 Basel, Switzerland

(72) Inventor(s):
Andreas Hotter
Arthur Pichler

(74) Agent and/or Address for Service:
Sandoz GMBH
Biochemiestrasse 10, A-6250 Kundl, Tirol, Austria

(51) INT CL:
C07D 495/04 (2006.01) ***A61K 31/4365*** (2006.01)
A61P 7/02 (2006.01)

(56) Documents Cited:
EP 2003136 A1 **WO 2010/070677 A2**
WO 2009/130289 A1 **WO 2009/129983 A1**
WO 2009/098142 A1

(58) Field of Search:
INT CL **A61K, A61P, C07D**
Other: **BIOSIS, CAS-ONLINE, EPODOC, INTERNET, MEDLINE, TXTE & WPI**

(54) Title of the Invention: **New crystal form**
Abstract Title: **Novel crystalline form of Prasugrel hydrogensulphate**

(57) Crystalline form III of Prasugrel hydrogensulphate. A process for the preparation of this new crystal form, pharmaceutical compositions comprising the same and use of the new crystal form as a pharmaceutical, in particular as a blood platelet aggregation inhibitor. Seed crystals which can be employed in the above mentioned process as well as a process for their preparation are also disclosed.

GB 2469883 A

Figure 1

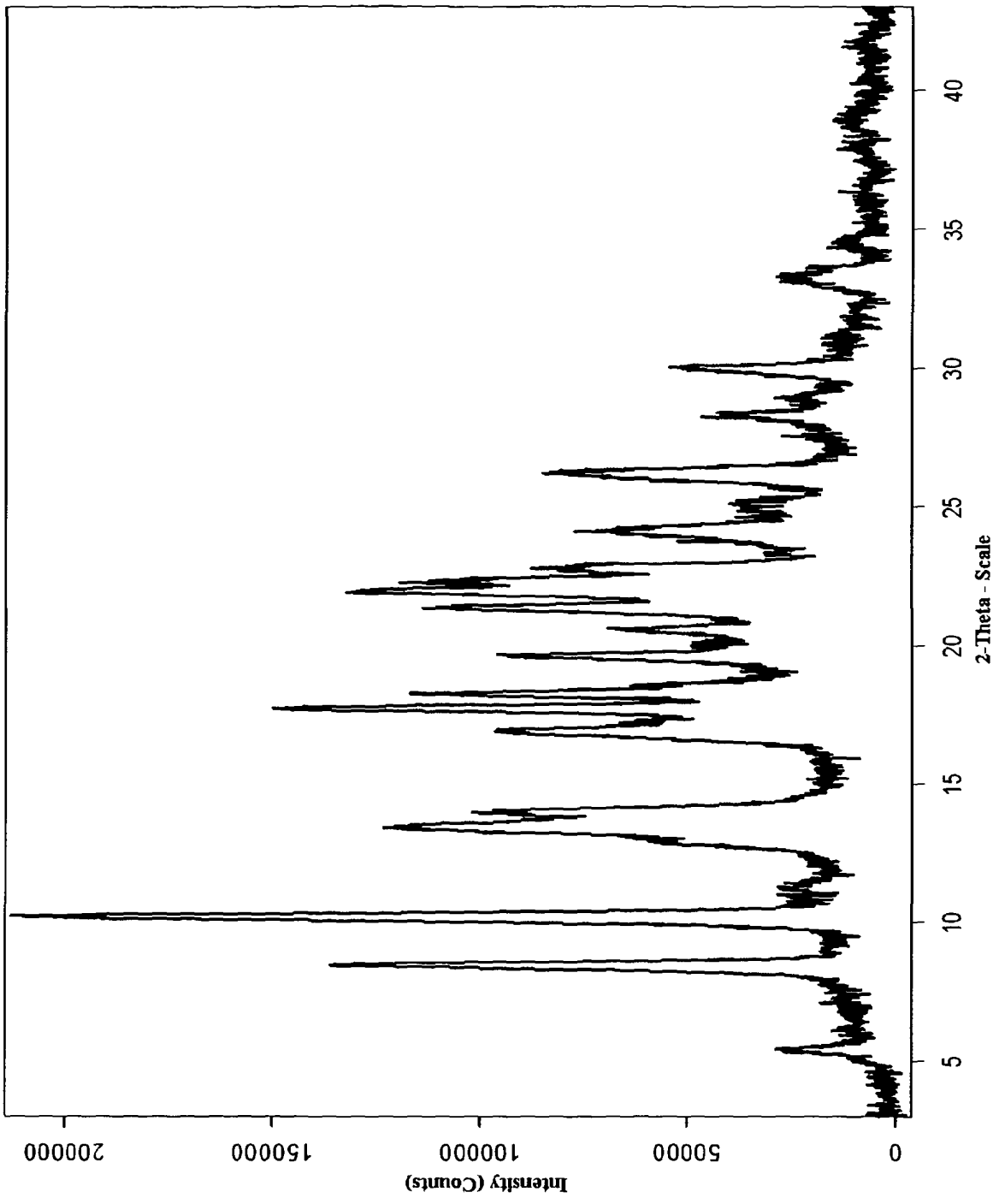
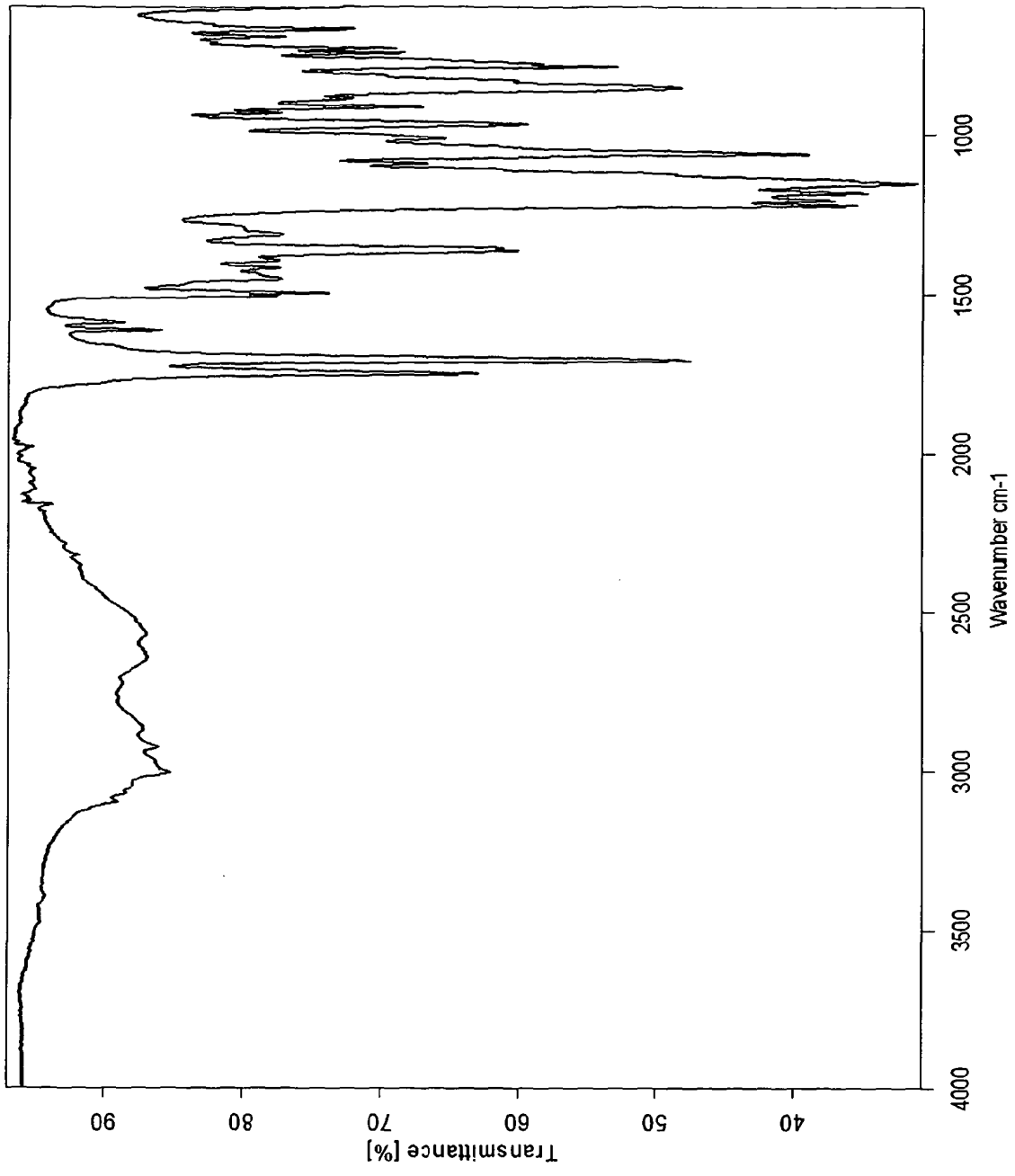

Intensity (Counts)
0
50000
100000
150000
200000
2-Theta - Scale
5
10
15
20
25
30
35
40

Figure 2


Transmittance [%]
90
80
70
60
50
40
Wavenumber cm-1
4000
3500
3000
2500
2000
1500
1000

NEW CRYSTAL FORM

FIELD OF THE INVENTION

The present invention relates to crystalline form III of the hydrogensulfate salt of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine. A process for the preparation of the new crystal form, pharmaceutical compositions comprising the same and the use of the new crystal form as a pharmaceutical, in particular as a blood platelet aggregation inhibitor are also described. Seed crystals which can be employed in the above mentioned process as well as a process for their preparation are also disclosed.

BACKGROUND OF THE INVENTION

Prasugrel, 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, is a thienopyridine derivative and acts as an antiplatelet agent. The platelet activation and subsequent platelet aggregation play an essential role in the pathogenesis of cardiovascular diseases. A former clinical study could demonstrate that Prasugrel is orally active and produces a potent antiplatelet and antithrombotic action with a rapid onset and long duration *via* platelet ADP receptors antagonisms. Prasugrel is a prodrug, which means it generates an active metabolite *in vivo* (Sugidachi A., Asai F., Ogawa T., et al., "The in vivo pharmacological profile of CS-747, a novel antiplatelet agent with platelet ADP receptor antagonist properties", Br. J. Pharmacol. 2000, **129**:1439-1446).

US 6,693,115 claims that acid addition salts of Prasugrel are useful as therapeutic or prophylactic agents for thrombus formation-induced or embolization-induced diseases. Prasugrel hydrochloride and Prasugrel maleate are disclosed in US 6,693,115. Furthermore a Prasugrel besylate is mentioned in WO 2007/114526.

Polymorphism is a phenomenon relating to the occurrence of different crystal forms for a single compound. There may be several different crystalline forms for the same molecule with distinct crystal structures and varying in physical properties like melting point, XRPD spectrum and IR-spectrum. These polymorphs are thus distinct solid forms which share the molecular formula of the compound from which the crystals are made up, however they may have distinct advantageous physical properties which can have a direct effect on the ability to

process and/or manufacture the drug substance and on the drug product, like flowability, as well as on drug product stability, dissolution, and bioavailability.

One important solid state physical property of a pharmaceutical compound is its dissolution rate in aqueous fluids. Since particular polymorphs of a pharmaceutically active compound may have different solubility properties, it is essential to identify the existence of polymorphs for providing pharmaceuticals with predictable solubility profiles. As the solubility influences the bioavailability of a pharmaceutically active compound this solid state property may have an impact on the therapy. Therefore, it is desirable to investigate all solid state forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms can be distinguished by X-ray diffraction spectroscopy and by other methods, e.g. infrared spectrometry.

There remains a need for alternative acid addition salts of Prasugrel and of particular solid state forms thereof having improved physicochemical properties.

SUMMARY OF THE INVENTION

The present invention relates to crystalline form III of Prasugrel hydrogensulfate. Therefore, in one embodiment, the present invention provides crystalline form III of Prasugrel hydrogensulfate.

Crystalline form III of Prasugrel hydrogensulfate can be characterized by an X-ray powder diffraction pattern comprising peaks at 2-theta angles of 5.4 ± 0.2°, 8.4 ± 0.2°, 10.2 ± 0.2°, 13.4 ± 0.2°, 13.9 ± 0.2°, 16.9 ± 0.2°, 17.7 ± 0.2°, 18.2 ± 0.2°, 19.6 ± 0.2°, 20.6 ± 0.2°, 21.3 ± 0.2°, 21.9 ± 0.2°, 24.1 ± 0.2°, 26.2 ± 0.2°, 28.2 ± 0.2° and 30.0 ± 0.2°.

Alternatively crystalline form III of Prasugrel hydrogensulfate can be described by an infrared spectrum comprising peaks at wavenumbers of 1751 ± 2 cm^{-1}, 1710 ± 2 cm^{-1}, 1364 ± 2 cm^{-1}, 1221 ± 2 cm^{-1}, 1060 ± 2 cm^{-1}, 1206 ± 2 cm^{-1}, 1012 ± 2 cm^{-1}, 854 ± 2 cm^{-1}, 788 ± 2 cm^{-1}.

In another embodiment the present invention provides a pharmaceutical composition comprising crystalline form III of Prasugrel hydrogensulfate. The pharmaceutical composition can be used for inhibiting blood platelet aggregation.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill from the following description. It should be understood, however, that the description and the following specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the description and the other parts of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: X-ray powder diffraction pattern of crystalline form III of Prasugrel hydrogensulfate

Figure 2: Infrared spectrum of crystalline form III of Prasugrel hydrogensulfate

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to crystalline form III of Prasugrel hydrogensulfate.

Crystalline form III of Prasugrel hydrogensulfate can be characterized by an X-ray powder diffraction pattern having peaks at 2-theta angles of 5.4 ± 0.2°, 8.4 ± 0.2°, 10.2 ± 0.2°, 13.4 ± 0.2°, 13.9 ± 0.2°, 16.9 ± 0.2°, 17.7 ± 0.2°, 18.2 ± 0.2°, 19.6 ± 0.2°, 20.6 ± 0.2°, 21.3 ± 0.2°, 21.9 ± 0.2°, 24.1 ± 0.2°, 26.2 ± 0.2°, 28.2 ± 0.2° and 30.0 ± 0.2°. A characteristic X-ray powder diffraction pattern of crystalline form III of Prasugrel hydrogensulfate is shown in Figure 1.

Table 1: X-Ray Powder Diffraction (XRPD) pattern of crystalline form III of Prasugrel hydrogensulfate

Angle [°2-theta ± 0.2°]	relative intensity [%]
5.4	13.6
8.4	64.0
10.2	100.0
13.4	57.6
13.9	47.7
16.9	45.1
17.7	70.0
18.2	54.6

19.6	45.1
20.6	32.8
21.3	53.2
21.9	62.0
24.1	36.2
26.2	39.6
28.2	21.8
30.0	25.3

In addition, crystalline form III of Prasugrel hydrogensulfate may be characterized by an infrared spectrum having characteristic bands at 1751, 1710, 1364, 1221, 1060, 1206, 1012, 854 and 788 cm^{-1}. A usual deviation for these bands is ± 2 cm^{-1}. A typical IR spectrum is shown in Figure 2.

A process for the preparation of crystalline form III of Prasugrel hydrogensulfate comprising the steps of:

(a) heating a mixture of Prasugrel or a salt or a derivative thereof, sulfuric acid and optionally a solvent to a temperature of about 35 °C or more;

(b) keeping the temperature at about 30-40 °C;

(c) adding seed crystals of form III; and

(d) isolating crystalline form III of Prasugrel hydrogensulfate

is also subject matter of the present invention.

Seed crystals of form III may be prepared according to Example 1 of the present invention. Example 2 describes the preparation of crystalline form III of Prasugrel hydrogensulfate.

For preparing crystalline form III of Prasugrel hydrogensulfate the Prasugrel starting material is heated in step (a) with sulfuric acid. The starting material can be Prasugrel itself or a salt thereof, in particular an acid addition salt of Prasugrel with an acid having a pKa of about 2 or more, such as the maleate salt, or another derivative thereof. Prasugrel, certain salts and derivatives can be prepared according to known procedures such as those mentioned in EP-A-542 411 or US-B-6,693,115.

Any suitable sulfuric acid can be used in step (a). Either diluted or concentrated sulfuric acid having a concentration in the range from about 5 to about 98 % can be employed. Preferably concentrated sulfuric acid, i.e. sulfuric acid having a concentration of about 95 to about 98 %, is used.

The ratio of Prasugrel to sulfuric acid can vary. Typically about 0.8 to about 5.0 equivalents, preferably about 0.9 to about 2.0 equivalents and more preferably about 1.0 to about 1.2 equivalents of sulfuric acid to 1 equivalent of Prasugrel (mol : mol) will be employed.

The Prasugrel starting material and the sulfuric acid are optionally in admixture with a solvent. Any type of solvent can be employed as long as it does not adversely effect the formation of the desired crystalline form III. Examples of suitable solvents are ketones such as acetone, methyl ethyl ketone or diethyl ketone and esters such as ethyl acetate, propyl acetate and butyl acetate. The solvent is preferably selected from ketones. Acetone is the most preferred solvent.

The Prasugrel starting material is preferably used in a concentration in the range from about 30 to about 500 g/l, more preferably about 100 to about 250 g/l, most preferably in a concentration of about 125 g/l if a solvent is employed.

After the crystallization, crystalline form III of Prasugrel hydrogensulfate can be isolated from the mixture. Any conventional method such as filtration, centrifugation or evaporation of the solvent can be employed. If necessary, the crystals can be purified further by recrystallization.

The crystalline form III of Prasugrel hydrogensulfate according to the present invention can be employed to treat or prevent any of the disorders which can be treated by Prasugrel or any of the other salts of Prasugrel. It is envisaged that it can also be employed to treat disorders which are indicated for the related compound Clopidogrel.

In particular, it can be employed for treating or preventing a disorder selected from the group consisting of thrombosis, embolism, coagulation induced vascular diseases and recurrence thereof and for use as an adjunct to percutaneous coronary intervention procedures. Furthermore, it can be used for preventing atherothrombotic events after myocardial infarction, after stroke, in patients having established peripheral arterial disease or in patients having Acute Coronary Syndrome.

Crystalline form III of Prasugrel hydrogensulfate can be administered alone or in combination with other pharmaceutically active compounds such as acetyl salicylic acid. The crystalline form III of Prasugrel hydrogensulfate and the other pharmaceutically active compound can be administered either simultaneously or sequentially.

The formulation of crystalline form III of Prasugrel hydrogensulfate is not particularly limited and it can be formulated according to known principles, e.g. either alone or together with pharmaceutically acceptable carriers, excipients, diluents and the like.

The crystalline form III of Prasugrel hydrogensulfate can be administered according to any appropriate route. Typically it will be administered orally or parenterally, preferably orally. Preferred formulations are liquid aqueous preparations for oral use (e.g. oral solutions, oral emulsions, oral suspensions, powders and granules for oral solutions and suspensions, oral drops, powder for oral drops, syrups, powders and granules for syrups), soluble tablets and parenteral preparations (e.g. injections, for example subcutaneous injections, infusions, concentrates for injections or infusions, powders for injections or infusions, gels for injections, implants).

Typical formulations and indications for Prasugrel are described, for example, in US 6,693,115, WO 2006/135605, WO 2007/024472, US 2007/0203157, EP-A-1 310 245, WO 97/17064, US 2007/0003628, WO 2005/048992, and WO 2007/113857. In those references relating to Clopidogrel, it is to be understood that Clopidogrel is to be replaced by the crystalline form III of Prasugrel hydrogensulfate according to the present invention. It is to be noted that these patents and patent applications are given as an example only and that this list is not to be considered exhaustive.

The present invention is illustrated in the following examples, which should not be construed as limiting.

EXAMPLES

The powder diffractogram was collected on a Unisantis XMD 300 X-ray powder diffractometer with a position sensitive detector in parallel beam optics using the following acquisition conditions: tube anode: Cu, 40 kV, 0.8 mA; 3 – 43° theta/2-theta; simultaneous detection of regions of 10° per step with detector resolution 1024, counting time 300 seconds per step. Samples were measured at room temperature in a standard sample holder on a rotating sample spinner. A typical precision of the 2-theta values is in the range of ± 0.2° 2-

theta. Thus a diffraction peak that appears at 5.0° 2-theta can appear between 4.8 and 5.2° 2-theta on most X-ray diffractometers under standard conditions.

The infrared spectrum was collected on a diamond ATR cell with an Bruker Tensor 27 FTIR spectrometer with 4 cm^{-1} resolution at ambient conditions. To collect a spectrum a spatula tip of a sample was applied to the surface of the diamond in powder form. Then the sample was pressed onto the diamond with a sapphire anvil and the spectrum was recorded. A spectrum of the clean diamond was used as background spectrum. A typical precision of the wavenumber values is in the range of ± 2 cm^{-1}. Thus an infrared peak that appears at 1716 cm^{-1} can appear between 1714 and 1718 cm^{-1} on most infrared spectrometers under standard conditions.

Example 1: Preparation of seed crystals of form III

100 mg Prasugrel and 1.0 eq. (15 µl) concentrated sulfuric acid (95-97 %) were dissolved in 1 ml acetone at about 40 °C. The solution was stored at -25 °C for 21 hours without stirring, whereas precipitation of a white solid occurred. The solvent was removed and the solid was dried at room temperature under vacuum for 19 hours to obtain a mixture of amorphous Prasugrel hydrogensulfate and crystalline form III of Prasugrel hydrogensulfate.

Example 2: Preparation of form III of Prasugrel hydrogensulfate

1 g Prasugrel and 1.2 eq (178 µl) concentrated sulfuric acid (95-97%) were dissolved in 10 ml acetone at 35 °C. To the solution seed crystals of form III, e.g. obtained from Example 1, were added while the temperature was kept at 35 °C. The mixture was stirred at 35 °C for 22 hours. The obtained solid was filtered off, washed with acetone and dried at room temperature under vacuum for 6 hours to obtain crystalline form III of Prasugrel hydrogensulfate.

CLAIMS

1. Crystalline form III of Prasugrel hydrogensulfate having an X-ray powder diffraction pattern comprising peaks at 2-theta angles of 5.4 ± 0.2°, 8.4 ± 0.2°, 10.2 ± 0.2°, 13.4 ± 0.2°, 13.9 ± 0.2°, 16.9 ± 0.2°, 17.7 ± 0.2°, 18.2 ± 0.2°, 19.6 ± 0.2°, 20.6 ± 0.2°, 21.3 ± 0.2°, 21.9 ± 0.2°, 24.1 ± 0.2°, 26.2 ± 0.2°, 28.2 ± 0.2° and 30.0 ± 0.2°.

2. Crystalline form III of Prasugrel hydrogensulfate having an infrared spectrum comprising peaks at wavenumbers of 1751 ± 2 cm^{-1}, 1710 ± 2 cm^{-1}, 1364 ± 2 cm^{-1}, 1221 ± 2 cm^{-1}, 1060 ± 2 cm^{-1}, 1206 ± 2 cm^{-1}, 1012 ± 2 cm^{-1}, 854 ± 2 cm^{-1} and 788 ± 2 cm^{-1}.

3. A process for the preparation of crystalline form III of Prasugrel hydrogensulfate comprising the steps of:
   (a) heating a mixture of Prasugrel or a salt or a derivative thereof, sulfuric acid and optionally a solvent to a temperature of about 35 °C or more;
   (b) keeping the temperature at about 30-40 °C;
   (c) adding seed crystals of form III; and
   (d) isolating crystalline form III of Prasugrel hydrogensulfate.

4. A pharmaceutical composition comprising crystalline form III of Prasugrel hydrogensulfate according to claim 1 or 2 and optionally a pharmaceutically acceptable carrier.

5. Crystalline form III of Prasugrel hydrogensulfate according to claim 1 or 2 for use as a medicament.

Application No:	GB0908006.0	**Examiner:**	Dr Bill Thomson
Claims searched:	1-5	**Date of search:**	4 August 2010

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
A	-	WO 2009/130289 A1 (SANDOZ AG) - See whole document, in particular page 2, line 17 - page 3, line 17 and the Examples
A	-	WO 2009/098142 A1 (HELM AG) - See whole document, in particular page 3, lines 10-16; page 6, line 24 - page 7, line 18 and the Examples
A	-	WO 2009/129983 A1 (RATIOPHARM GMBH) - See whole document, in particular page 1, lines 1-3; page 2, lines 8-13, Tables 1 and 2 and the Examples
A	-	EP 2003136 A1 (DAIICHI SANKYO COMPANY, LTD. & UBE INDUSTRIES, LTD.) - See whole document, in particular paragraphs 1-7 and 12-21
A	-	WO 2010/070677 A2 (GLENMARK GENERICS LIMITED) - See whole document, in particular page 3, lines 25-28 and page 7, line 4-page 8, line 3

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

Worldwide search of patent documents classified in the following areas of the IPC

A61K; A61P; C07D

The following online and other databases have been used in the preparation of this search report

BIOSIS, CAS-ONLINE, EPODOC, INTERNET, MEDLINE, TXTE & WPI

International Classification:

Subclass	Subgroup	Valid From
C07D	0495/04	01/01/2006
A61K	0031/4365	01/01/2006
A61P	0007/02	01/01/2006